Synthesis and Antimicrobial Activity of *N*-(Substituted)-*N′*-(2,3-dihydro-2-oxido-5-benzoyl-1*H*-1,3,2-benzodiazaphosphol-2-yl) Ureas

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***N*-(Substituted)-*N′*-(2,3-dihydro-5-benzoyl-2-oxido-1*H*-1,3,2-benzodiazaphosphol-2-yl) ureas were synthesized by reacting 3,4-diaminobenzophenone (4) with different chlorides of carbamidophosphoric acids (3) in the presence of triethylamine at 40—45 °C. Their ^{1}H-, ^{13}C- and ^{31}P-NMR spectral data are discussed. The title compounds were screened for antifungal and antibacterial activity against the fungi *Aspergillus niger* and *Fusarium solani* and bacteria *Escherichia coli* and *Staphylococcus aureus*. These compounds showed higher antibacterial activity when compared with antifungal activity.**

Key words 3,4-diamino benzophenone; isocyanatophosphonic dichloride; carbamidophosphoric acid dichloride

Extensive investigation of compounds containing P–N linkages by numerous research groups have led to many interesting and far reaching developments.[1] Organophosphorus heterocycles bearing P–N functionality have shown pesticidal and medicinal activity.[2—6] Benzimidazol-2-yl-carbamates have proven anthelmintic activity.[7,8] In continuation of our research interests, several new classes of substituted ureas of the type RR′P(O)NHC(O)NHR″ were synthesized and characterized by spectral data and they were also screened for their antifungal and antibacterial activity.

Results and Discussion

Addition of equivalent amounts of isocyanatophosphonic dichloride[9,10] (**1**) to various amines (**2**) at −15 °C in dry toluene led to the corresponding carbamido phosphoric acid dichloride (**3**). When equimolar quantities of 3,4-diaminobenzophenone (**4**) reacted with carbamido phosphoric acid dichloride (**3a**—**i**) in dry toluene–tetrahydrofuran mixture (1 : 1) in the presence of triethylamine at 40—45 °C (Chart 1), the title compounds were formed. Purifications of **5a**—**i** were achieved by filtering off triethylamine hydrochloride, evaporation of the filtrate, washing the residue with water and recrystallization of the residue from methanol. Their structures were established by elemental analyses, IR, ^{1}H-, ^{13}C- and ^{31}P-NMR spectral data (Tables 1—3).

Reaction yields, elemental analyses, IR and ^{31}P-NMR data of **5a**—**i** are given in Table 1. Tables 2 and 3 contain ^{1}H- and ^{13}C-NMR spectral data. The IR spectra of **5a**—**i**[11]

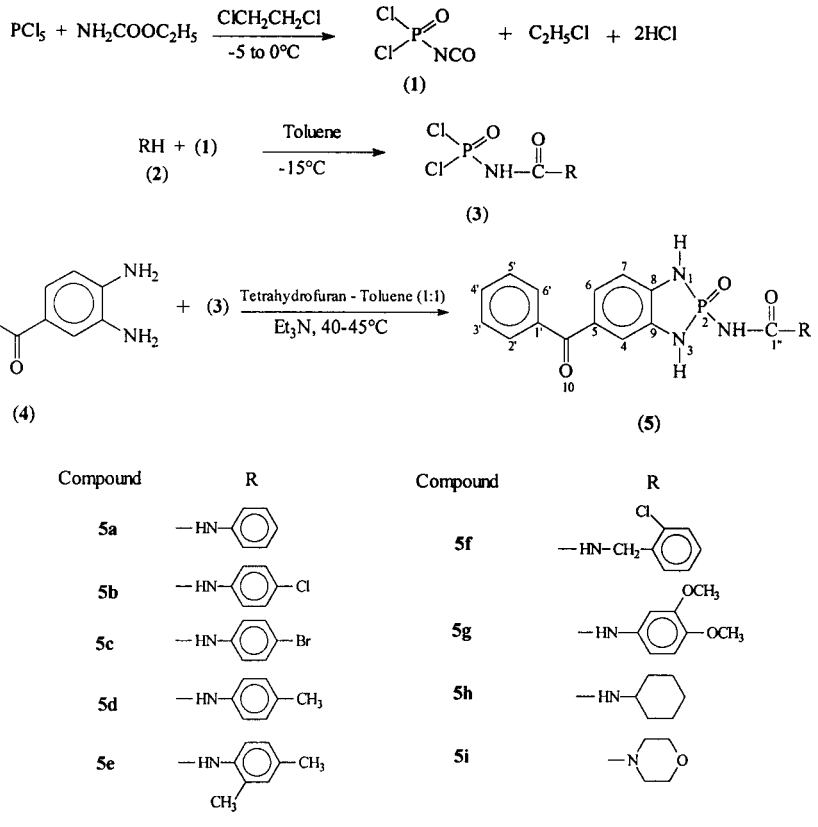

Chart 1

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Table 1. Physicochemical, IR and ^{31}P-NMR Spectral Data of **5a**—**i**

Compound	mp (°C)	Yield[a]	Molecular formula	Elemental analyses Calcd/Found			IR (cm^{-1})[b]				^{31}P-NMR data[c,d] (ppm)
				C	H	N	ArCOAr	P=O	P–NH	NH–CO	
5a	145—147 (dec)	54	$C_{20}H_{17}N_4PO_3$	61.22 61.54	4.36 4.10	14.27 14.69	1618	1278	3369	1659	−11.20, 1.36
5b	142—144 (dec)	59	$C_{20}H_{16}N_4PO_3Cl$	56.28 55.69	3.77 3.45	13.12 13.56	1626	1260	3340	1655	—
5c	151—153 (dec)	56	$C_{20}H_{16}N_4PO_3Br$	50.97 50.48	3.42 3.06	11.89 11.25	1603	1303	3329	1636	−8.32
5d	69—71	60	$C_{21}H_{19}N_4PO_3$	62.06 —	4.71 —	13.78 —	1601	1307	3317	1656	−11.53
5e	158—160 (dec)	52	$C_{22}H_{21}N_4PO_3$	62.85 62.43	5.03 5.28	13.32 13.84	1630	1283	3361	1660	−11.88, 1.28
5f	136—138 (dec)	51	$C_{21}H_{18}N_4PO_3Cl$	57.21 57.68	4.11 4.56	12.70 12.36	1624	1283	3361	1662	−11.45, 1.19
5g	165—167 (dec)	58	$C_{22}H_{17}N_4PO_5$	58.40 —	4.67 —	12.38 —	1613	1229	3348	1672	−11.48
5h	194—196 (dec)	46	$C_{20}H_{23}N_4PO_3$	60.29 59.78	5.81 5.46	14.06 13.52	1625	1284	3371	1654	—
5i	164—166 (dec)	47	$C_{18}H_{19}N_4PO_3$	55.96 —	4.96 —	14.50 —	1617	1260	3372	1664	—

a) Recrystallized from methanol. *b*) Recorded as KBr pellets. *c*) Recorded in dimethyl sulfoxide-d_6. *d*) Chemical shifts in ppm from 85% phosphoric acid.

Table 2. ^{1}H-NMR Data[a,b] of **5a**—**i**

Compound	H (4, 6 & 7)	Ar–H	Ar–CH_3/Ar–OCH_3	P–NH	–NHC(O)	C(O)NH–
5a	7.16 (s, 1H, 4-H) 6.92 (d, 8.1 Hz, 6-H) 7.28 (d, 8.0 Hz, 7-H)	7.39—7.86 (m, 10H)	—	6.04 (s, 2H)	9.42 (br s, 1H)	8.68 (br s, 1H)
5b	7.14 (s, 1H, 4-H) 7.07 (d, 8.8 Hz, 6-H) 7.29 (d, 8.6 Hz, 7-H)	7.46—7.91 (m, 9H)	—	5.94 (s, 2H)	9.58 (br s, 1H)	8.72 (br s, 1H)
5c	7.25 (s, 1H, 4-H) 6.77 (d, 8.5 Hz, 6-H) 7.55 (d, 7.2 Hz, 7-H)	7.68—7.95 (m, 9H)	—	5.93 (s, 2H)	— 	8.24 (br s, 1H)
5d	7.01 (s, 1H, 4-H) 6.75 (d, 7.3 Hz, 6-H) 7.26 (d, 6.9 Hz, 7-H)	7.35—7.75 (m, 9H)	2.21 (s, 3H)	6.39 (s, 2H)	9.64 (br s, 1H)	8.42 (br s, 1H)
5e	7.23 (s, 1H, 4-H) 6.64 (d, 8.2 Hz, 6-H) 7.07 (d, 8.1 Hz, 7-H)	7.48—7.64 (m, 8H)	2.20 (s, 3H) 2.51 (s, 3H)	5.73 (s, 2H)	— 	—
5f	7.06 (s, 1H, 4-H) 6.50 (d, 8.1 Hz, 6-H) 6.96 (d, 8.1 Hz, 6-H)	7.16—7.59 (m, 9H) 4.16 (s, 2H, NH–C<u>H</u>$_2$)	—	4.78 (s, 2H)	9.43 (br s, 1H)	9.24 (br s, 1H)
5g	6.84 (s, 1H, 4-H) 6.68 (d, 8.0 Hz, 6-H) 7.13 (d, 8.0 Hz, 7-H)	7.29—7.74 (m, 8H)	3.76 (s, 3H) 3.74 (s, 3H)	5.51 (s, 2H)	9.60 (br s, 1H)	8.34 (br s, 1H)
5h	7.10 (s, 1H, 4-H) 6.92 (d, 8.4 Hz, 6-H) 7.31 (d, 8.3 Hz, 7-H)	7.42—7.73 (m, 5H) 1.26—1.89 (m, 11H)	—	6.12 (2, 2H)	— 	—
5i	7.17 (d, 1.9 Hz, 4-H) 6.60 (d, 8.1 Hz, 6-H) 6.93 (d, 8.0 Hz, 7-H)	7.52—7.68 (m, 5H) 3.22—3.56 (m, 8H, C<u>H</u>$_2$)	—	5.54 (2,2H)	— 	8.10 (br s, 1H)

a) Chemical shifts in δ and J (Hz) given in parentheses. *b*) Recorded in dimethyl sulfoxide-d_6.

(Table 1) showed bands at 3317—3372 (P–NH), 1601—1630 (Ar–<u>CO</u>–Ar), 1229—1303 (P=O) and 1636—1672 (–NH–<u>CO</u>) cm^{-1}.

The ^{1}H-NMR spectra of **5a**—**i**[12] (Table 2) showed singlets for H-4 at 6.84—7.25 ppm, the doublets at 6.60—7.07 ppm (J=7.3—8.0 Hz) for H-6; the other doublets found at 6.93—7.55 ppm (J=6.9—8.6 Hz) were attributed to H-7. The arylcarbamido and benzoyl moieties in **5a**—**i** exhibited multiplets in the range of 7.16—7.95 ppm. The proton in the P–NHC=O appeared at extreme downfield, at 9.42—9.64 ppm as a singlet when compared to the other three NH protons. It is of interest to note that phosphorus coupling is

limited to P–NH protons only and not extended to other protons of carbamido moiety. The NH proton signals were confirmed by D_2O exchange experiments.

The ^{13}C-NMR chemical shifts (Table 3) were recorded for some members of the title compounds (**5b**, **d**—**g**). The chemical shifts for C-4, C-5, C-6 and C-7 appeared at 113.5—115.8, 135.9—138.1, 125.2—125.9 and 116.7—119.9 respectively. In the case of C-1′, C-(2′, 6′), C-4′ and C-(3′, 5′) the range of chemical shifts was 138.0—139.3, 129.3—129.8, 131.1—131.6 and 128.7—129.3, respectively. The nitrogen bearing C-8 and C-9 exhibited signals in the down field at 143.1—144.8 and 137.9—138.9. The signal for the carbonyl of the carbamido function C-(1″) is observed at 148.4—154.7 ppm, while the signals for the benzoyl carbonyl group C(10) occurred at 193.6—194.6 ppm. The chemical shifts could not be identified in the ^{13}C-NMR spectra of **5a**, **c**, **h** and **i** because of the poor quality of the spectrum due to their meagre solubility in DMSO.

Table 3. ^{13}C-NMR Data[a—c] of **5a**—**i**

Carbon atoms	5b	5d	5e	5f	5g
C(1′)	139.2	138.0	139.3	138.9	138.1
C(2′, 6′)	129.8	129.5	129.7	129.3	129.5
C(4′)	131.5	131.3	131.1	131.1	131.6
C(3′, 5′)	128.7	129.0	129.3	128.8	129.2
C(10)	193.8	194.1	194.6	193.6	194.4
C(4)	115.2	115.7	115.8	113.5	114.3
C(5)	135.9	136.1	136.2	137.0	138.1
C(6)	125.6	125.2	125.8	125.9	125.2
C(7)	117.4	118.6	118.5	119.9	116.7
C(8)	144.8	144.2	144.1	143.1	143.6
C(9)	137.9	138.0	138.2	138.9	138.1
C(1″)	154.6	153.4	154.7	153.4	148.4
C(2″)	144.1	144.2	144.1	137.0	132.3
C(3″)	116.2	114.7	124.6	135.3	131.6
C(4″)	129.3	130.1	130.8	128.3	143.6
C(5″)	124.4	126.4	127.3	127.1	104.2
C(6″)	129.3	130.1	125.4	125.9	121.9
C(7″)	116.2	114.7	114.9	130.2	112.0
C″(CH_3)	—	20.1	21.1	—	—
			18.5		
C″(OCH_3)	—	—	—	—	55.6
					55.2
Methylene carbon	—	—	—	79.6	—

a) Chemical shifts in ppm. *b*) Recorded in dimethyl sulfoxide-d_6. *c*) **5a**, **c**, **h** and **i** gave unresolved spectra due to poor solubility.

The ^{31}P-NMR chemical shifts[13] of these compounds (**5**) appeared in the range of −11.88 to 1.36 ppm. Compounds **5a**, **e** and **f** showed two signals.

Antimicrobial Activity The compounds **5a**—**i** (Table 4) were screened at two different concentrations (25, 75 μg/disc) for their antifungal activity on *Fusarium solani* and *Aspergillus niger*, Nystatin (25 μg/disc) is used as standard according to disc-diffusion method.[14] The fungal cultures were grown on potato dextrose broth at 25 °C for 3 d and finally spore suspension was adjusted to 10^6 spores/ml. Their antibacterial activity was evaluated against *Staphylococcus aureus* and *Escherichia coli* (10^5 cell/ml) on nutrient agar plates at 37 °C for 24 h.[15] Vancomycin (25 μg/disc) and gentamycin (25 μg/disc) were used as standard antibiotics. The title compounds were potent against tested fungi and bacteria. The compounds showed higher antibacterial activity when compared with antifungal activity.

Experimental

The melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 unit. ^{1}H- and ^{13}C-NMR spectra were recorded on AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. The compounds were dissolved in DMSO-d_6. The chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P).

3,4-Diamino benzophenone (**4**) was procured from Aldrich Chemical Company, Inc., U.S.A. and was used without further recrystallization.

Table 4. Antimicrobial Activity of **5a**—**i**

Compound	Concentration (μg/disc)	Zone of inhibition (mm)[b]			
		Fungi		Bacteria	
		Aspergillus niger	*Fusarium solani*	*Staphylococcus aureus*	*Escherichia coli*
5a	25	2	—	3	2
	75	4	—	6	3
5b	25	1	—	5	2
	75	3	—	8	5
5c	25	—	—	4	3
	75	—	—	10	8
5d	25	1	2	3	2
	75	3	4	7	6
5e	25	2	—	3	9
	75	6	—	8	12
5f	25	—	—	2	3
	75	—	—	5	6
5g	25	1	—	4	5
	75	2	—	9	9
5h	25	—	1	5	4
	75	—	2	3	9
5i	25	1	2	3	5
	75	3	8	6	9
Standards[a]	25	4	8	10	8

a) Nystatin (25 μg/disc) for *Aspergillus niger* and *Fusarium solani*, vancomycin (25 μg/disc) for *Staphylococcus aureus* and gentamycin (25 μg/disc) for *Escherichia coli.* *b*) Diameter of filter paper is 16 mm, compounds **5a**—**i** tested in 20% *N*,*N*-dimethylformamide. "—" indicates no activity.

Preparation of *N*-Phenyl-*N′*-(2,3-dihydro-2-oxido-5-benzoyl-1*H*-1,3,2-benzodiazaphosphol-2-yl) Urea (5a) A solution of aniline (0.186 g, 0.002 mol) in dry toluene (20 ml) was added dropwise over a period of 20 min to a cold solution (−15 °C) of isocyanatophosphonic dichloride (**1**, 0.320 g, 0.002 mol) in dry toluene (20 ml). After the addition, the temperature of the reaction mixture was allowed to rise slowly to room temperature and was maintained further for 2 h. Phenyl carbamidophosphoric acid dichloride (**3a**) being insoluble in toluene separated out. To this mixture was added a cold solution (0 °C) of 3,4-diaminobenzophenone (**4**, 0.424 g, 0.002 mol) and triethylamine (0.404 g, 0.004 mol) in 30 ml of tetrahydrofuran–toluene mixture (1 : 1). The temperature of the reaction mixture was raised slowly 40—45 °C and kept under stirring for 4—5 h. The precipitated triethylamine hydrochloride was filtered off and the solvent from the filtrate was evaporated under reduced pressure. The residue after washing with water was recrystallized from methanol to afford a pure material of (**5a**) as an amorphous powder, yield 0.42 g (54%) mp 145—147 °C (dec.). The other compounds (**5b**—**i**) were prepared by adopting the same procedure.

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